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(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS FOR TREATING HEPATITIS C INFECTIONS

(57) Abstract

The present invention relates to novel biheterocyclic derivatives which are serine protease inhibitors; the pharmaceutically acceptable salts and *N*–oxides thereof; their uses as therapeutic agents and the methods of their making.

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# NOVEL COMPOUNDS AND COMPOSITIONS FOR TREATING HEPATITIS C INFECTIONS

This application claims the benefit under 35 U. S. C. 119(e)(1) of prior filed provisional application 60/103,085 filed October 5, 1998.

Field of the Invention:

The present invention relates to a novel class of compounds which are effective in inhibiting the activity of serine proteases, particularly the hepatitis C virus protease NS3, and in treating hepatitis C viral infections. The present invention also relates to methods for using the compounds in treating hepatitis C viral infections and methods for making and pharmaceutical compositions containing the compounds.

Description of the Field:

Viral hepatitis is a hepatocellular inflammatory disease caused by specific hepatotrophic viruses. The disease can range from acute hepatitis progressing to chronic persistent hepatitis and eventual cirrhosis. Parenterally transmitted non-A, non-B viral infections cause 90 to 95% of all transfusion-associated viral hepatitis and may account for as many as 300,000 cases of hepatitis per year in the United States. Hepatitis C virus (HCV) is the apparent causative agent for most non-A, non-B hepatitis infections and is most likely the leading cause of chronic liver disease in the Western world.

The HCV genome encodes for a single polypeptide having approximately 3010 amino acids. Five nonstructural regions, NS1 to NS5, are encoded toward the 3'-end of the genome and several structural proteins are encoded near the 3'-end of the genome. The NS3 region encodes for a serine protease that, along with an associated cofactor NS4A, is involved in processing the HCV translation product into its individual functioning structural and nonstructural proteins. Hence, functional NS3 protease is a necessary component of HCV replication.

Patients with acute HCV hepatitis may recover without medical intervention.

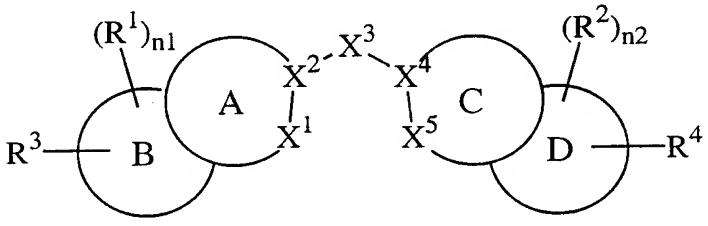
However, about half of all acute infections progress to chronic persistent hepatitis, which left untreated can lead to cirrhosis and eventual death. The hepatocellular inflammatory effects of the chronic HCV hepatitis can be ameliorated with corticosteroid treatments. Antiviral agents such as acyclovir or interferon-α are used to treat HCV infection. Interferon-α, the only approved anti-HCV therapeutic agent, is expensive and must be administered by subcutaneous injection three times a week for up to six months. Interferon-α produces improvements in liver enzymes and histology; however, HCV RNA titer frequently remains high despite long term chemotherapy. Moreover, a significant population of patients relapse when drug therapy is stopped. The overall success in treating HCV hepatitis with interferon-α is about 25%.

Agents which inhibit the processing of viral protein can be effective anti-viral agents. Hence, the NS3 serine protease is a rational target for designing new and effective anti-HCV chemotherapies. Peptide-like NS3 protease inhibitors are known and described in PCT International Applications WO 98/17679 and WO 98/22496 as anti-HCV chemotherapeutic agents. The discovery and development of low molecular weight, non-peptide inhibitors of the NS3 serine protease will provide a highly effective means for treating HCV infections.

The disclosures of documents, including patents and patent applications, referred to throughout this application are incorporated herein by reference.

## SUMMARY OF THE INVENTION

This application relates to a compound of Formula I:




I

in which:

n1 is 0, 1, 2, 3 or 4;

n2 is 0, 1, 2 or 3;

A together with B comprise a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom moiety, $X^1$ and $X^2$ are adjacent annular members of an aromatic ring and $X^1$ is a heteroatom moiety selected from –N=, $–NR^5–$, –O– and –S–, wherein $R^5$ is hydrogen or $(C_{1-6})$alkyl;

C together with D comprise a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, $X^4$ and $X^5$ are adjacent annular members of an aromatic ring and $X^5$ is a heteroatom moiety selected from –N=, $–NR^6–$, –O– and –S–, wherein $R^6$ is hydrogen or $(C_{1-8})$alkyl optionally substituted with one to two substituents independently selected from halo, tri$(C_{1-6})$alkylammonio, $–NR^7R^7$, $–C(O)NR^7R^7$, $–OR^7$, $–C(O)OR^7$, $–OC(O)R^7$ or $–S(O)_2OR^7$, wherein $R^7$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl;

$X^3$ is –O–, –S–, –S(O)–, $–S(O)_2–$, –C(O)–, $–NR^8–$ or $–CR^8R^9–$, wherein $R^8$ is hydrogen, halo, $(C_{1-6})$alkyl or together with $R^9$ forms $(C_{2-6})$alkylene or $(C_{1-6})$alkylidene and $R^9$ is hydrogen, halo, $(C_{1-6})$alkyl or as defined above, wherein any 1 to 3 carbon atoms with a free valence comprising $R^8$ and/or $R^9$ optionally independently are substituted with halo, tri$(C_{1-6})$alkylammonio, $–NR^{10}R^{10}$, $–C(O)NR^{10}R^{10}$, $–OR^{10}$, $–C(O)OR^{10}$ or $–OC(O)R^{10}$, wherein $R^{10}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl;

$R^1$ at each occurrence independently is $(C_{1-6})$alkyl, $(C_{1-6})$alkyloxy, $(C_{1-6})$alkanoyloxy, $(C_{1-6})$alkylthio, halo, hydroxy or mercapto and bonded to any annular carbon atom with a free valence comprising B;

$R^2$ at each occurrence independently is $(C_{1-6})$alkyl, $(C_{1-6})$alkyloxy, $(C_{1-6})$alkanoyloxy, $(C_{1-6})$alkylthio, halo, hydroxy or mercapto and bonded to any annular carbon atom with a free valence comprising C;

$R^3$ is cyano, $–R^{11}$, $–CR^{12}R^{12}NR^{11}R^{13}$, $–C(NR^{13})R^{11}$, $–C(O)R^{11}$, $–C(NR^{13})NR^{11}R^{13}$, $–C(O)NR^{11}R^{13}$, $–C(O)OR^{11}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–S(O)_2NR^{11}R^{13}$ or $–S(O)_2OR^{11}$ and bonded to

any annular atom with a free valence comprising B, wherein:

$R^{11}$ is hydrogen, $(C_{1-6})$alkyl, cyclo$(C_{3-6})$alkyl$(C_{0-3})$alkyl, heterocyclo$(C_{3-6})$alkyl$(C_{0-3})$alkyl, $(C_{6-10})$aryl$(C_{0-3})$alkyl, hetero$(C_{5-14})$aryl$(C_{0-3})$alkyl, polycyclo$(C_{9-10})$aryl$(C_{0-3})$alkyl or heteropolycyclo$(C_{8-10})$aryl$(C_{0-3})$alkyl; wherein any alkyl moiety comprising $R^{11}$ optionally independently is substituted with 1 to 3 substitutents selected from $-P(O)(OR^{14})OR^{14}$, $-S(O)_2OR^{14}$ and $-C(O)OR^{14}$ and any 1 to 3 annular carbon atoms with free valences of any aromatic ring comprising $R^{11}$ optionally independently are substituted with halo, nitro, cyano, optionally halo-substituted $(C_{1-6})$alkyl, $-OR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-X^6NR^{14}R^{14}$, $-X^6NR^{14}C(O)NR^{14}R^{14}$ or $-X^6NR^{14}C(NR^{14})NR^{14}R^{14}$, wherein $X^6$ is a bond or methylene and $R^{14}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl,

$R^{12}$ at each occurrence independently is hydrogen, $(C_{1-3})$alkyl or together with another $R^{12}$ and the carbon atom to which both are attached forms cyclopropyl and

$R^{13}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl; and

$R^4$ is $-R^{15}$, $-OR^{15}$, $-NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2OR^{15}$, $-S(O)_2NR^{15}R^{16}$, $-N(R^{16})S(O)_2R^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-N(R^{16})C(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-N(R^{16})C(O)OR^{15}$ or $-N(R^{16})C(O)NR^{15}R^{16}$, and bonded to any annular carbon atom with a free valence comprising C, wherein:

$R^{15}$ is $(C_{1-6})$alkyl substituted with 1 to 2 radicals selected from $-P(O)(OR^{17})OR^{17}$ and $-S(O)_2OR^{17}$ and optionally substituted with 1 to 2 radicals $-C(O)OR^{17}$ groups, wherein $R^{17}$ is hydrogen or $(C_{1-6})$alkyl, and

$R^{16}$ is hydrogen or $(C_{1-6})$alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

A second aspect of this invention is a pharmaceutical composition which contains a compound of the invention or a *N*-oxide derivative, prodrug derivatives, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

A third aspect of this invention is a method of treating a patient infected with hepatitis

C virus, which method comprises administering to the patient a therapeutically effective amount of a compound of the invention or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

A fourth aspect of this invention is the processes for preparing compounds of the invention and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof as set forth in "Detailed Description of the Invention".

## DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this application and have the meanings given below:

"Alkanoyl" means the radical –C(O)R, wherein R is alkyl as defined in the Detailed Description of the Invention, having overall the number of carbon atoms indicated (e.g., $(C_{1-6})$alkanoyl includes the radicals formyl, acetyl, propionyl, butyryl, isobutyryl, crotonoyl, isocrotonyl, etc.).

"Alkyl", for the purposes of this application, means a straight or branched, saturated or unsaturated aliphatic hydrocarbon radical having the number of carbon atoms indicated, and any ketone, thioketone or iminoketone thereof (e.g., $(C_{1-8})$alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, 3-oxopentyl, 3-thioxopentyl, 3-iminopentyl, etc.). The term "$(C_0)$alkyl", as in $(C_{6-10})$aryl$(C_{0-3})$alkyl, means that the linking alkyl moiety does not exist and the aryl group is bonded directly to the point of attachment as a subsitutent.

"Alkylene" means a saturated or unsaturated hydrocarbon divalent radical having the number of carbon atoms indicated and any ketone, thioketone, iminoketone derivative thereof (e.g., $(C_{2-6})$alkylene includes methylene (–$CH_2$–), ethylene (–$CH_2CH_2$–), methylethylene,

vinylene, ethynylene, trimethylene ($-CH_2CH_2CH_2-$), 2-oxotrimethylene ($-CH_2C(O)CH_2-$), 2-thiatrimethylene ($-CH_2C(S)CH_2-$), 2-iminotrimethylene ($-CH_2C(NH)CH_2-$), propenylene ($-CH_2CH=CH-$ or $-CH=CHCH_2-$), propanylylidene ($=CHCH_2CH_2-$ ), propendiylene ($=CHCH=CH-$), tetramethylene, pentamethylene, etc.).

"Alkylidene" means the radical $=CRR$, wherein each R independently is hydrogen or alkyl, as defined in the Detailed Description of the Invention, having overall the number of carbon atoms indicated (e.g., $(C_{1-6})$alkylidene includes methylidene, ethylidene, propylidene, isopropylidene, etc.).

"Alkyloxy" means the radical $-OR$, wherein R is alkyl as defined in the Detailed Description of the Invention, having the number of carbon atoms indicated (e.g., $(C_{1-6})$alkyloxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, vinyloxy, allyloxy, 1-propenyloxy, isopropenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 2-methylallyloxy, ethynyloxy, 1-propynyloxy, 2-propynyloxy, etc.).

"Ammonio" means the radical $-NH_3^+$.

"Amino" means the radical $-NH_2$.

"Aryl" means an aromatic monocyclic or fused polycyclic hydrocarbon radical containing the number of carbon atoms indicated, wherein each ring contained therein is comprised of 6 annular members (e.g., $(C_{6-14})$aryl includes phenyl, naphthyl, anthracenyl, phenanthrenyl, etc.).

"Carbamoyl" means the radical $-C(O)NH_2$.

"Carboxy" means the radical $-C(O)OH$.

"Cyano" means the radical $-CN$.

"Cycloalkyl" means a saturated or unsaturated, monocyclic or fused polycyclic hydrocarbon radical containing the number of carbon atoms indicated, wherein each ring contained therein is comprised of 3 to 8 annular members, and any carbocyclic ketone, thioketone and iminoketone derivative thereof. For example, $(C_{3-14})$cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, and the like.

"Deprotecting" refers to removing any protective groups present after the selective reaction has been carried out.

"Fused heterobicyclic radical" means a heterocyclic radical containing two fused rings having the number of annular members indicated, wherein at least two annular members of one ring are common to the second ring, and the carbocyclic ketone and thioketone derivatives thereof. For examplea heterobicyclic radical containing from 8 to 12 annular atoms includes 1*H*-benzimidazol-2-yl, 1*H*-naphtho[2,3-*d*]imidazol-2-yl, 1*H*-imidazo[4,5-*f*]quinolin-2-yl, 1*H*-imidazo[4,5-*b*]pyridin-2-yl, 2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl, 2,6-dithioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl, 7*H*-purin-8-yl, 1,6-dihydrocyclopentaimidazol-2-yl, 4-quinolin-2-yl, and the like.

"Free valence", when referring to atoms in the compounds of the invention, means that the atom(s) referred has the capacity to form a bond with another molecule, other than hydrogen, and, thus, comprise a substituted atom. For the purposes of the this application, when referring to a compound of the invention by formula and the attachement of a free valence not designated, it is to be understood that the reference is to all attachments possible, including to hydrogen, optional bonds or optional substituents. Hence, for example, the compound of Formula II, infra., in which the annullar atom $X^8$ is N, refers to instances wherein the indicated nitrogen atom is attached to an annular carbon atom (i.e., when the optional bond is present) and a hydrogen atom (i.e., when the optional bond is absent).

"Halo" means fluoro, chloro, bromo or iodo.

"Heteroatom moiety", unless indicated otherwise, means a moiety selected from –N=, $-NR^{18}-$, –O–, –S–, –S(O)–, $-S(O)_2-$ and $-P(O)(OR^{18})-$, wherein $R^{18}$ is hydrogen or $(C_{1-6})$alkyl.

"Heteroaryl" means an aromatic monocyclic or fused polycyclic divalent radical having the number of annular atoms indicated, wherein each ring contained therein is comprised of 5 to 6 annular members and one or more of the annular atoms is a heteroatom moiety, as defined in the Detailed Description of the Invention, and each ring contained therein is comprised of 5 to 6 annular members (e.g., hetero$(C_{5-14})$aryl includes thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxaxolyl, indolyl, benzo[*b*]thienyl, isobenzofuranyl, purinyl, isoquinolyl, pterdinyl, perimidinyl, imidazolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, etc.).

"Heterocycloalkyl" means cycloalkyl, as defined above, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety, as defined in the Detailed Description of the Invention, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the term heterocyclo($C_{5-14}$)alkyl includes piperidyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, quinuclidinyl, morpholinyl, and the like.

"Heterocycloalkylene" means cycloalkylene, as defined above, except one or more of the annular carbon atoms indicated is replaced by a heteroatom moiety, as defined in the Detailed Description of the Invention, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the term heterocyclo($C_{3-14}$)alkylene includes piperidylene, pyrrolidinylene, pyrrolinylene, imidazolidinylene, quinuclidinylene, morpholinylene, and the like.

"Heteropolycycloaryl" means polycycloaryl, as defined below, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety, as set defined in the Detailed Description of the Invention, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, heteropolycyclo($C_{8-10}$)alkyl includes 3,4-dihydro-2*H*-quinolinyl, 5,6,7,8-tetrahydroquinolinyl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, and the like.

"Hydroxy" means the radical –OH.

"Iminoketone" means the derivative –C(NR)–, wherein R is hydrogen or alkyl as defined in the Detailed Description of the Invention.

"Isomers" mean compounds of the invention having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has $2^{n-1}$ enantiomeric pairs, where $n$ is the number of chiral

centers. Compounds with more than one chiral center may exist as either an individual diasteromer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog and the absolute descriptor *R* or *S* is cited in parenthesis followed by a hyphen and the chemical name of the compound. Compounds of the invention that contain a chiral center can exist as individual stereoisomers or mixtures of stereoisomers. For the purposes of the this application when referring to a compound of the invention by name or by formula and the configuration is not designated, it is to be understood that the reference is to all possible configurations of the compound and the mixtures, racemic or otherwise, thereof.

"Ketone" means the derivative –C(O)–.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes, halogen, hydroxy, alkyloxy, alkylsulfonloxy (e.g., mesyloxy, ethanesulfonyloxy, etc.), arylsulfonyloxy (e.g., benzenesulfonyloxy and tosyloxy, thienyloxy), dihalophosphinoyloxy, tetrahalophosphaoxy, and the like.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally independently are substituted with" means that the group referred to may or may not be substituted in order to fall within the scope of the invention.

"*N*-oxide derivatives" means derivatives of compounds of the invention in which nitrogens are in an oxidized state (i.e., O←N) and which possess the desired pharmacological activity. The *N*-oxide derivatives of compounds of the invention can be prepared by methods known to those of ordinary skill in the art.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor

otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of the invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Phosphono" means the radical $-P(O)(OH)_2$.

"Polycycloaryl" means a fused polycyclic radical containing the number of carbon atoms indicated, wherein at least one, but not all, of the fused rings comprising the radical is aromatic and each ring contained therein is comprised of five to six annular members, and any carbocyclic ketone and thioketone derivative thereof. For example, polycyclo($C_{9-10}$)aryl includes indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl,

2,4-dioxo-1,2,3,4-tetrahydronaphthyl, and the like.

"Prodrug derivatives" means derivatives of compounds of the invention which are converted *in vivo* to the corresponding non-derivatized form of a compound of the invention. Suitable prodrug derivatives include those compounds of the invention in which one or more nitrogen and/or oxygen atoms with a free valence are substituted with a group which is readily cleavable by *in vivo* processes. For example, prodrug derivatives of compounds of the invention may contain one or more *N*-substituted amino groups (e.g., $-NH_2(R^{19})$), *N*-substituted nitrogen atoms incorporated into an aliphatic, alicyclic or aromatic structure (e.g., $-N(R^{19})-$), *N*-substituted imino or amidino groups (e.g., $-C(NR^{19})H$, $-C(NR^{19})NH_2$ or $-C(NH)NHR^{19}$), *N*-substituted guanidino groups (e.g., $-NHC(NR^{19})NHR^{19}$, $-NHC(NH)NHR^{19}$ or $-NHC(NR^{19})NH_2$), and the like, in which $R^{19}$ is (i) $-C(O)R^{20}$ or $-CH(R^{21})OC(O)R^{20}$, wherein $R^{20}$ is $(C_{1-10})$alkyl, $(C_{1-10})$alkyloxy, carbamoyl, $(C_{1-10})$alkylcarbamoyl, di$(C_{1-10})$alkylcarbamoyl, *cis*-2-$(C_{1-10})$alkanoyloxyphenylvinyl, 3-$(C_{1-10})$alkanoyloxybutyryl, $(C_{3-10})$cycloalkyl, hetero$(C_{3-10})$cycloalkyl, $(C_{6-10})$aryl or hetero$(C_{5-10})$aryl and $R^{21}$ is hydrogen or $(C_{1-10})$alkyl; (ii) $-X^7-R^{22}$, wherein $X^7$ is $(C_{1-10})$alkylene and $R^{22}$ is carboxy; or (iii) $-C(O)OCH(R^{23})OC(O)R^{24}$, wherein $R^{23}$ is hydrogen, $(C_{1-10})$alkyl or $(C_{3-10})$cycloalkyl and $R^{24}$ is $(C_{1-10})$alkyl or $(C_{3-10})$cycloalkyl. In addition, prodrug derivatives of compounds of the invention may contain one or more *N*-hydroxylated imino or amidino groups (e.g., $-C(NOR^{25})H$, $-C(NOR^{25})NH_2$ or $-C(NH)NHOR^{25}$) or *N*-hydroxylated guanidino groups (e.g., $-NHC(NOR^{25})NH_2$, $-NHC(NH)NHOR^{25}$), in which $R^{25}$ is hydrogen, methyl, $-C(O)R^{26}$ or $-CH(R^{27})OC(O)R^{26}$, wherein $R^{26}$ is $(C_{1-10})$alkyl or $(C_{3-10})$cycloalkyl and $R^{27}$ is hydrogen or $(C_{1-10})$alkyl; *N*-substituted hydroxy groups (e.g.,$-OR^{28}$), in which $R^{28}$ is $-C(O)R^{19}$ or $-CH(R^{20})OC(O)R^{19}$, wherein $R^{19}$ and $R^{20}$ are as defined above; and/or ester derivatives of carboxylic acids (e.g., $-C(O)OR^{29}$), phosphonic acids (e.g., $-P(O)(OR^{29})$) and sulfonic acids (e.g., $-S(O)_2OR^{29}$ wherein $R^{29}$ is $(C_{1-10})$alkyl, $(C_{3-10})$cycloalkyl or $-C(O)OCH(R^{23})OC(O)R^{24}$, wherein $R^{23}$ and $R^{24}$ are as defined above.

"Protective group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., a group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected

reactive site and which can be readily removed after the selective reaction is completed.

"Protected derivatives" means derivatives of compounds of the invention in which a reactive site or sites are blocked with protective groups. Protected derivatives of compounds of the invention are useful in the preparation of compounds of the invention. Suitable protective groups for reactive nitrogen atoms include *tert*-butoxycarbonyl, benzyloxycarbonyl and any other suitable amino protective groups (e.g., see T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981).

"Therapeutically effective amount" means that amount which, when administered to a patient is effective for treating a disease.

"Thioketone" means the derivative –C(S)–.

"Treatment" or "treating" refers to any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in a patient which may be predisposed to the disease but does not yet experience or display the pathology or symptoms of the disease,

(2) inhibiting the disease, i.e., arresting development of its pathology and/or symptoms, or

(3) ameliorate the disease, i.e., reversing its pathology and/or symptoms.

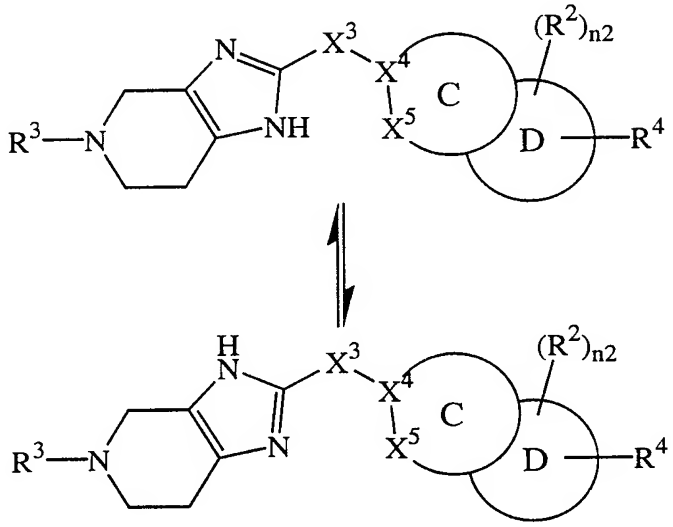
"Sulfo" means the radical –S(O)OH.

The compounds of the invention and the intermediates and starting materials are named by AUTONOM Version 2.0 by Beilstein-Institut and Springer-Verlag Berlin Heidelberg, a fully automatic computerized system for assigning IUPAC systematic nomenclature directly from the structural diagrams of organic compounds.. For example, a compound of Formula I in which:

A together with B comprise 1*H*-benzoimidazol-2-yl, C together with B comprise 6-(1-carboxy-2-phosphonoethylcarbamoyl)-1-methyl-1*H*-benzoimidazol-2-yl and $X^3$ is $-CH_2(CH_3)-$ is named 2-({2-[1-(1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid.

Certain compounds of the invention exist in tautomeric equilibrium. For example,

compounds of Formula I in which A together with B comprise 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl exist in equilibrium between tautomers of the following formulae:



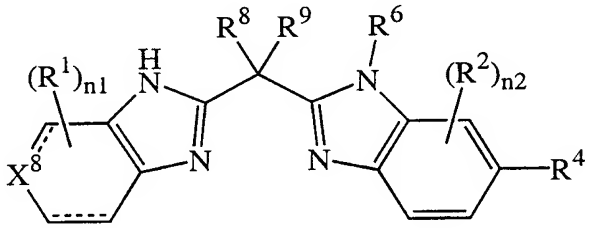
and, hence, while the compounds of this invention may be named, illustrated or otherwise described in this application as one possible tautomer, it is to be understood that all possible tautomers are meant to be encompassed by such names, illustrations and descriptions. Thus, the name 2-({2-[1-(5-hexylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid is meant to include its tautomer 2-({2-[1-(6-hexylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid.

Presently Preferred Embodiments:

While the broadest definition of this Invention is set forth in the Summary of the Invention, certain aspects of the Invention are preferred. A preferred aspect of the Invention is a compound of Formula I in which A together with B and C together with D comprise fused heterobicyclic radicals wherein A and C each contain 5 annular members and B and D

each contain 6 annular members and $X^1$ and $X^2$ and $X^4$ and $X^5$ are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring.

A preferred aspect of the Invention are compounds of Formula II:



II

in which:

the dashed lines independently represent optional bonds;

n1 is 0, 1, 2, 3 or 4;

n2 is 0, 1, 2 or 3;

$X^8$ is C, N, $CR^3$ or $NR^3$, wherein $R^3$ is cyano, $(C_{1-6})$alkyl, $-C(O)R^{11}$, $-C(O)NR^{11}R^{13}$ or $-C(O)OR^{11}$, wherein $R^{11}$ independently is hydrogen, $(C_{1-6})$alkyl or $(C_{1-4})$aryl$(C_{0-4})$alkyl, $R^{13}$ is hydrogen or $(C_{1-6})$alkyl and any alkyl moiety comprising $R^{11}$ optionally independently is substituted with 1 to 3 substitutents selected from $-P(O)(OR^{14})OR^{14}$, $-S(O)_2OR^{14}$ and $-C(O)OR^{14}$, wherein $R^{14}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl; provided that when $X^8$ is $NR^3$ the adjacent optional bond is not present and, unless indicated otherwise, any free valence of an annular atom is occupied by a hydrogen atom;

$R^1$ and $R^2$ at each occurrence independently are $(C_{1-6})$alkyl, $(C_{1-6})$alkyloxy, halo or hydroxy and bonded to any annular carbon atom with a free valence;

$R^4$ is $-C(O)NR^{15}R^{16}$, wherein:

$R^{15}$ is $(C_{1-6})$alkyl substituted with 1 to 2 radicals selected from $-P(O)(OR^{17})OR^{17}$ and $-S(O)_2OR^{17}$ and optionally substituted with 1 to 2 $-C(O)OR^{17}$ groups, wherein $R^{17}$ is hydrogen or $(C_{1-6})$alkyl, and

$R^{16}$ is hydrogen or $(C_{1-6})$alkyl;

$R^6$ is $(C_{1-6})$alkyl optionally substituted with one to two substituents independently selected from halo, tri$(C_{1-6})$alkylammonio, $-NR^7R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-C(O)OR^7$,

$-OC(O)R^7$ or $-S(O)_2OR^7$, wherein $R^7$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl; and

$R^8$ and $R^9$ independently are hydrogen, halo or $(C_{1-6})$alkyl, wherein any 1 to 3 carbon atoms with a free valence comprising $R^8$ and/or $R^9$ optionally independently are substituted with halo, tri$(C_{1-6})$alkylammonio, $-NR^{10}R^{10}$, $-C(O)NR^{10}R^{10}$, $-OR^{10}$, $-C(O)OR^{10}$ or $-OC(O)R^{10}$, wherein $R^{10}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl.

A preferred aspect of the invention are compounds of Formula II in which both of the optional bonds are present, n1 and n2 each are 0, $X^8$ is N or $CR^3$, $R^6$ is $(C_{1-4})$alkyl, $R^8$ is hydrogen or methyl and $R^9$ is hydrogen; preferably wherein $R^3$ is acetyl, benzyloxycarbonyl, cyano or $-C(O)NR^{11}R^{13}$, wherein $R^{11}$ and $R^{13}$ independently are hydrogen or methyl.

A preferred aspect of the invention are compounds of Formula II in which neither of the optional bonds are present, n1 and n2 are 0, $X^8$ is $NR^3$, $R^6$ is $(C_{1-4})$alkyl, $R^8$ is hydrogen or methyl and $R^9$ is hydrogen; preferably wherein $R^3$ is acetyl, benzyloxycarbonyl or $-C(O)NR^{11}R^{13}$, wherein $R^{11}$ and $R^{13}$ independently are hydrogen or methyl.

A preferred aspect of the invention are compounds of Formula II in which both of the optional bonds are present, n1 is 0, 1, 2, 3 or 4; n2 is 0; $X^8$ is C; $R^1$ at each occurrence is chloro, fluoro or hydroxy; $R^6$ is $(C_{1-4})$alkyl; $R^8$ is hydrogen or methyl; and $R^9$ is hydrogen.

Pharmacology and Utility:

The compounds of the invention are serine protease inhibitors and/or are intermediates useful in the preparation of the compounds of the invention. In particular, the compounds inhibit HCV protease NS-3 and, as such, are useful in treating HCV infections. Methods for testing the compounds of the invention for their serine protease inhibitory activity are known in the art. Typically, these methods measure the enzyme-induced hydrolysis of peptide-based fluorogenic substances. Details of an exemplary procedure for measuring NS3 inhibitory activity are described in Example 25, infra.

The compounds of the invention may be administered alone to treat patients with HCV infections or in combination with other anti-viral agents such as α-, β- or γ-interferons, ribavirin, amantadine and the like.

Compositions and Administration:

In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of the invention may range from 1 microgram per kilogram body weight (μg/kg) per day to 10 milligram per kilogram body weight (mg/kg) per day, typically 10 μg/kg/day to 1 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from 80 μg/day to 100 mg/day, typically 0.1 mg/day to 10 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of the invention for treating a given patient.

The compounds of the invention can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of the invention in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable

solutions, include water, saline, aqueous dextrose and glycols.

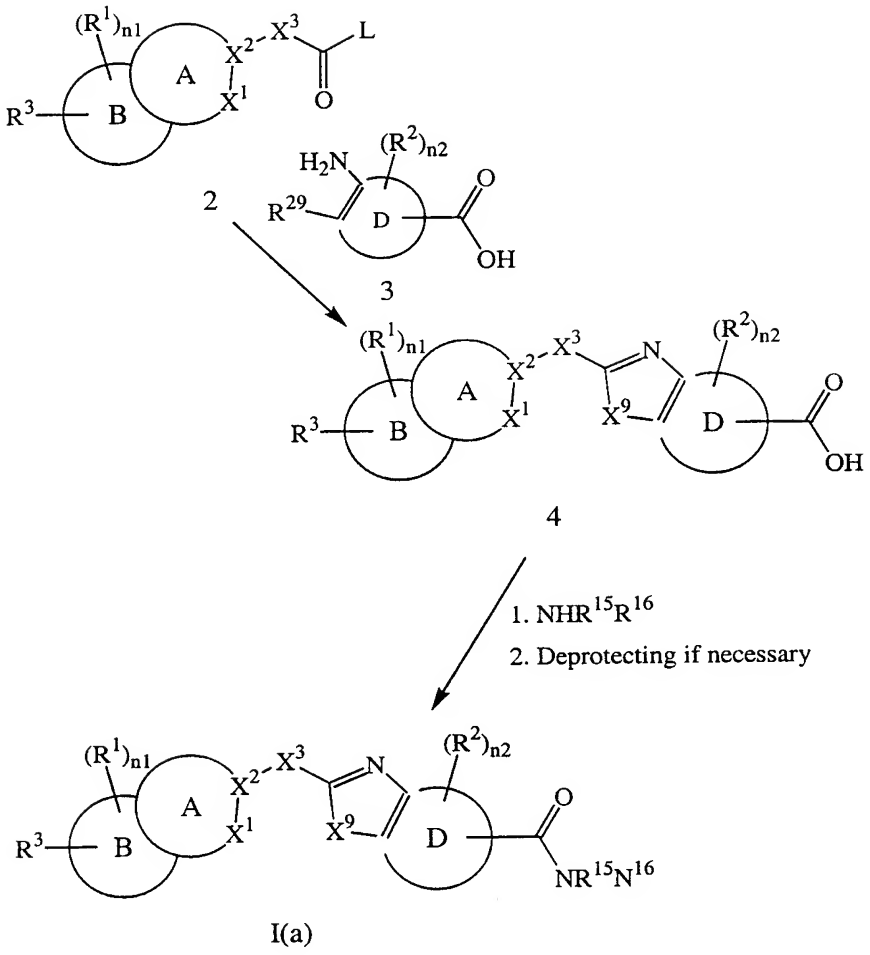
The amount of a compound of the invention in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of the invention for treating an infection will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of the invention are described in Example 26.

Chemistry:

Generally, the compounds of the present invention are synthesized using standard techniques and reagents known to and used by those of skill in the art. It will be noted that the linkages between the various functional groups generally comprise carbon linked to the nitrogen of an amide or carbamate, the oxygen of a carbamate or the carbon of a carbonyl. Those of skill in the art will recognize that methods and reagents for forming these bonds are well known and readily available. *See*, *e.g.*, March, ADVANCED ORGANIC CHEMISTRY, 4th Ed. (Wiley 1992), Larock, COMPREHENSIVE ORGANIC TRANSFORMATIONS (VCH 1989); and Furniss, *et al.*, VOGEL'S TEXTBOOK OF PRACTICAL ORGANIC CHEMISTRY 5th ed. (Longman 1989), each of which is incorporated herein by reference.

In particular, compounds of Formula I in which $X^4$ and $X^5$ are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring and $R^4$ is $-C(O)N(R^{13})R^{12}$, can be prepared by the methods depicted in the following reaction scheme:

Scheme 1




I(a)

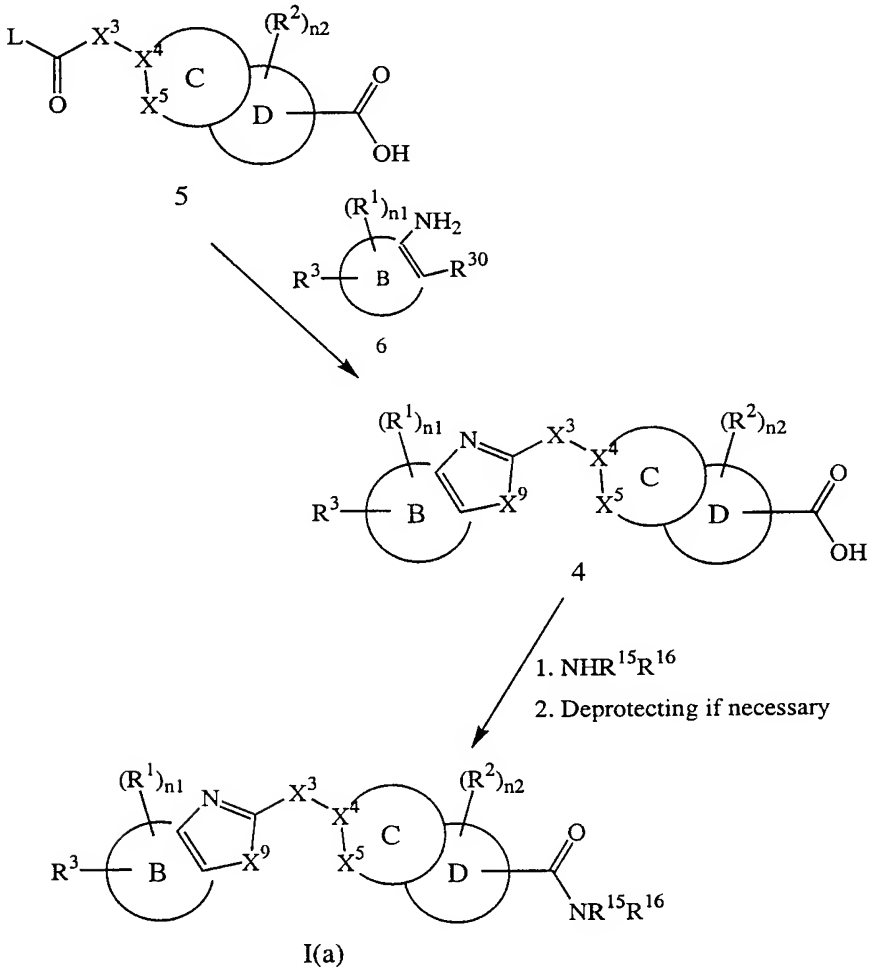
in which L is a leaving group, D together with the vinylene moiety to which it is fused comprise a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and each annular atom optionally is a heteroatom, $R^{29}$ is –OH, –$NHR^6$ or –SH, $X^9$ is –O–, –$NR^6$– or –S– and n2, n3, n4, A, B, $X^1$, $X^2$, $X^3$, $X^5$, $R^1$, $R^2$, $R^3$, $R^4$ and $R^6$ are as defined in the Summary of the Invention.

Compounds of Formula I in which $X^4$ and $X^5$ are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring (Formula I(a)) can be prepared by reacting a compound of Formula 1, or a protected derivative thereof, with a compound of Formula 2, or a protected derivative thereof, and then deprotecting if necessary. The reaction between the compounds

of Formulae 1 and 2 may be carried out neat, but preferably is carried out in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or polyphosphoric acid, at 160 to 200°C, preferably 180-190°C, and requires 1 to 5 hours to complete. Deprotection can be effected by any means which removes the protective group and gives the desired product in reasonable yield.

In a similar fashion, compounds of Formula I in which $X^1$ and $X^2$ adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring can be prepared by the methods depicted in the following reaction scheme:

Scheme 2



in which L is a leaving group, $R^{30}$ is –OH, –$NHR^5$ or –SH, $X^9$ is –O–, –$NR^5$– or –S– and n2, n3, n4, B, C, $X^1$, $X^3$, $X^4$, $X^5$, $R^1$, $R^2$, $R^3$, $R^4$ and $R^6$ are as defined in the Summary of the Invention.

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, high-pressure liquid chromatography (HPLC), or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can, of course, be used. Nuclear magnetic resonance (NMR) spectra were recorded on a General Electric "QE Plus" spectrometer (300 MHZ). Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Fourier Transform IR (FTIR). Analytical HPLC was performed on a Ultrafast Microprotein Analyzer, Michrom BioResources, Inc. equipped with a PLRP column, 1mm x 150mm. Preparative HPLC was performed on a Gilson LC using a VYDAC 1x25 cm $C_{18}$ reverse phase (RP) column or a Waters Prep LC2000 system using a Vydac 5x25 cm $C_{18}$ RP column. Mass spectra (MS) were obtained on a Finnigan SSQ 710 with an ESI source by direct infusion or by HPLC MS (Ultrafast Microprotein Analyzer, $C_{18}$ column 2mm X 150 mm). Unless otherwise noted, all reagents and equipment were either prepared according to published procedures or were purchased from commercial sources, such as Aldrich Chemical Co. (Milwaukee, WI), Sigma Chemical Co. (St. Louis, MO) and ICN Chemical Co. (Irvine, CA). The techniques used to perform the syntheses described below will be recognized by those of skill in the art as routine (*see, e.g.*, March, Larock, or Furniss, *supra*).

Additional Processes for Preparing Compounds of the Invention:

Compounds of the invention in which $R^3$ is carbamoyl can be prepared by treating a compound of the invention in which $R^3$ is cyano with acid (e.g., hydrobromic acid) in a suitable solvent (e.g., acetic acid) for 5 to 8 hours at room temperature, then adding water to the reaction mixture and allowing 2 to 3 days for formation of the corresponding amide.

The compounds of the invention may be prepared as pharmaceutically acceptable acid

addition salts by reacting the free base forms of a compound of The invention with a pharmaceutically acceptable inorganic or organic acid. Alternatively, the pharmaceutically acceptable base addition salts of the compounds of the invention may be prepared by reacting the free acid forms of compounds of the invention with pharmaceutically acceptable inorganic or organic bases. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of the invention are set forth in the definitions section of this application. Alternatively, the salt forms of the compounds of The invention may be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of The invention can be prepared from the corresponding base addition salt or acid addition salt form. For example, compounds of the invention in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, etc.). Compounds of The invention in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of the invention can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of The invention with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as methylene chloride) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of the invention can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of the invention in unoxidized form can be prepared from *N*-oxides of compounds of The invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, etc.) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, etc.) at 0 to 80°C.

Prodrug derivatives of the compounds of the invention can be prepared by methods

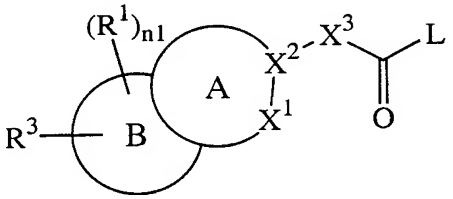
known to those of ordinary skill in the art. For further details on prodrugs and their preparation see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*. 4:1985)..

Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

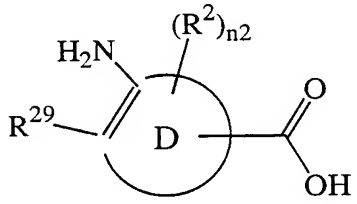
Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diasteromeric derivatives of compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

In summary, an aspect of this Invention is a process for preparing a compound of Formula I, which process comprises:

(a) reacting a compound of Formula 2:

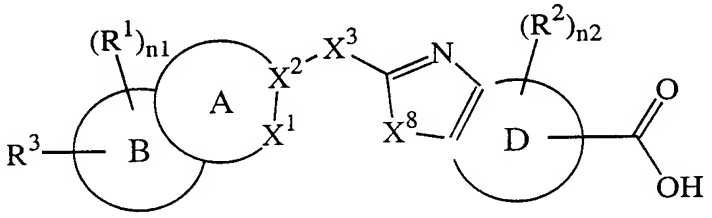


or a protected derivative thereof, with a compound of Formula 3:



3

or a protected derivative thereof, in which L is a leaving group, D together with the vinylene moiety to which it is fused comprise a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and each annular atom optionally is a heteroatom, $R^{29}$ is –OH, –$NHR^6$ or –SH and n1, n2, n3, A, B, $X^1$, $X^2$, $X^3$, $R^1$, $R^2$, $R^3$, $R^4$ and $R^6$ are as defined in the Summary of the Invention, to give a compound of Formula 4:



4

and then reacting the compound of Formula 4 with an amine of the formula $NHR^{12}R^{13}$ and deprotecting if necessary to give a compound of Formula I in which $X^4$ and $X^5$ are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring and $R^4$ is –$C(O)N(R^{13})R^{12}$;

(c) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt;

(d) optionally further converting a salt form of a compound of Formula I to non-salt form;

(e) optionally further converting an unoxidized form of a compound of Formula I into a

pharmaceutically acceptable *N*-oxide;

(f) optionally further an *N*-oxide form of a compound of Formula I its unoxidized form;

(g) optionally further converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(h) optionally further converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

Examples:

The following examples are provided merely for the purposes of illustration and are not to be construed in any way as limiting the scope of the present invention. Those skilled in the art will recognize that certain variations and modifications can be practiced within the scope of the invention.

EXAMPLE 1

3,4-Diamino-benzoic acid amide

3,4-Dinitro-benzoic acid amide (3.5 g, 16.6 mmol) was taken into methanol (100 mL and added to 10% palladium on carbon (1.0 g) under a nitrogen atmosphere. The mixture was then hydrogenated at 60 psi using a Parr apparatus over 8 hours. Filtration and concentration of the organic filtrate afforded 3,4-diamino-benzoic acid amide (2.5 g, 100%) as a tan solid; $^1$H-NMR (300 MHZ, $d_6$-DMSO): 7.40 (br s, 1H), 7.05 (d, 1H), 6.95 (dd, 1H), 6.70 (br s, 1H), 6.45 (d, 1H), 4.90 (br s, 2H), 4.50 (br s, 2H).

EXAMPLE 2

3-Ethoxy-3-iminopropionic acid ethyl ester hydrochloride

A 2 L three-neck flask, equipped with drying tube, was charged with ethyl cyanoacetate (200 mL, 1.67 mol), toluene (1 L) and anhydrous ethanol (175 mL). The reaction mixture was cooled to 0° C and sparged with hydrogen chloride gas for 1 hour. The

reaction mixture was then sealed and allowed to warm to ambient temperature followed by stirring an additional 18 hours. The reaction mixture was diluted with an excess of ethyl ether (2 L) and the resulting precipitate was collected by filtration then washed with additional ethyl ether to afford 3-ethoxy-3-iminopropionic acid ethyl ester hydrochloride (270 g, 83%) as a white solid; $^1$H-NMR (300 MHZ, $d_6$-DMSO): 7.69 (br s, 1H), 7.50 (br s, 1H), 4.50 (q, 2H), 4.11 (q, 2H), 3.98 (s, 2H), 1.30 (tr, 3H), 1.16 (tr, 3H).

## EXAMPLE 3

(5-Carbamoyl-1*H*-benzoimidazol-2-yl)-acetic acid ethyl ester

3,4-diamino-benzoic acid amide (756 mg, 5.0 mmol), prepared as in Example 1, was taken into glacial acetic acid (5 mL) followed by addition of 3-ethoxy-3-iminopropionic acid ethyl ester hydrochloride (1.47 g, 7.5 mmol), prepared as in Example 2, and the mixture was warmed to 70°C for one hour. The mixture was concentrated *in vacuo* and the residue partitioned with saturated aqueous sodium hydrogen carbonate (10 mL) and ethyl acetate (10 mL). A solid formed and an excess of ethyl ether was added to the suspension. Filtration and washing the solid with additional ethyl ether afforded (5-carbamoyl-1*H*-benzoimidazol-2-yl)-acetic acid ethyl ester (803 mg, 65%) as a grey solid; $^1$H-NMR (300 MHZ, $d_6$-DMSO): 8.10 (s, 1H), 7.95 (br s, 1H), 7.75 (d, 1H), 7.50 (d, 1H), 7.20 (br s, 1H), 4.10 (q, 2H), 4.00 (s, 2H), 1.20 (tr, 3H).

## EXAMPLE 4

3-Methylamino-4-nitro-benzoic acid

To a sealable tube was added 4-nitro-3-methoxy-benzoic acid (5.0 g, 25.4 mmol) and aqueous methylamine (40%, 15 mL). The tube was securely capped and placed in an oil bath heated at 100 °C. A blast shield was used for safety. The reaction mixture was heated for 12 hours and allowed to cool to room temperature. The orange product was precipitated by pouring the crude mixture into a stirring slurry of 1 M aqueous hydrochloric acid and ice.

The product was filtered and rinsed with water. Recrystallization from hot ethanol afforded 3-methylamino-4-nitro-benzoic acid (3.6 g, 73%) as a bright red crystalline solid; $^1$H-NMR (300 MHZ, $d_6$-DMSO): 13.5 (s, 1H), 8.3 (q, 1H), 8.2 (d, 1H), 7.4 (s, 1H), 7.1 (d, 1H), 3.0 (d, 3H).

## EXAMPLE 5

### 3-Methylamino-4-amino-benzoic acid

3-Methylamino-4-nitro-benzoic acid (5.0 g, 25.5 mmol), prepared as in Example 4, was taken up into a 2:1 methanol and tetrahydrofuran solution (300 mL) and added to 10% palladium on carbon (1 g) under a nitrogen atmosphere. The mixture was hydrogenated at 60 psi using a Parr apparatus over 8 hours. Filtration followed by concentration of the organic solution afforded 3-methylamino-4-amino-benzoic acid (4.2 g, 100%) as a brown solid; $^1$H-NMR (300 MHZ, $d_6$-DMSO): 7.10 (d, 1H), 6.90 (s, 1H), 6.50 (d, 1H), 5.25 (br s, 2H), 4.75 (br s, 1H), 2.65 (s, ,3H).

## Example 6

### 2-(5-Carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carboxylic acid

5-Carbamoyl-1*H*-benzoimidazol-2-yl-acetic acid ethyl ester (800 mg, 3.24 mmol), prepared as in Example 3, and 3-methylamino-4-amino-benzoic acid (540 mg, 3.24 mmol), prepared as in Example 5, were combined neat followed by addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU, 1 g) and the mixture was heated to 190° C under a nitrogen atmosphere for 1.5 hours. The homogeneous liquid was cooled to ambient temperature followed by addition of an excess of dichloromethane. Agitation of the mixture with warming afforded a grey precipitate which was collected by filtration and washed with additional dichloromethane to afford 2-(5-carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carboxylic acid (958 mg, 85%); $^1$H-NMR (300 MHZ,

$d_6$-DMSO): 8.30 (s, 1H), 8.21 (s, 1H), 8.19 (br s, 1H), 7.95 (d, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.45 (br s, 1H), 5.01 (s, 2H), 4.00 (s, 3H).

EXAMPLE 7

2-{[2-(5-Carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-phosphono-propionic acid

(Compound 1)

2-Amino-3-phosphonopropionic acid (56 mg, 0.33 mmol) and *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (1.0 mL, 5.4 mmol) were heated to 60° C under a nitrogen atmosphere for one hour to give a homogeneous solution of 2-amino-3-phosphonopropionic acid tris-trimethylsilyl ester. The solution was then concentrated *in vacuo* to a colorless oil and subsequently taken into DMF solution (0.5 mL). In a separate reaction vessel, 2-(5-carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carboxylic acid (115.3 mg, 0.33 mmol), prepared as in Example 6, in DMF solution cooled to 0° C, was sequentially treated with bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP, 153.8 mg, 0.33 mmol), diisopropylethylamine (0.12 mL, 0.67 mmol) and the previously generated DMF solution of 2-amino-3-phosphonopropionic acid tris-trimethylsilyl ester. The mixture was warmed to 40° C and stirred a total of 12 hours. Concentration *in vacuo* followed by treatment with trifluoroacetic acid (1 mL) afforded a homogeneous solution which was concentrated again. The residue was taken into 5% aqueous acetonitrile and the coupled product was purified by preparative reverse phase HPLC. Lyophillization of the pure fractions afforded 2-{[2-(5-carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-phosphono-propionic acid (32 mg, 18%) as an off white amorphous solid; plasma desorption LRMS: Calculated for $C_{21}H_{22}N_6O_7P$ ($MH^+$): 501.4, Found: 501.0.

Proceeding as in Example 7 and substituting different starting materials the following compounds of the invention were prepared:

2-({2-[1-(5-fluoro-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 2); plasma desorption LRMS: Calculated for $C_{21}H_{22}FN_5O_6P$ ($MH^+$): 490.4, Found: 490.0;

2-({2-[1-(5-hydroxy-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 3); plasma desorption LRMS: Calculated for $C_{21}H_{23}N_5O_7P$ ($MH^+$): 488.4, Found: 488.5;

2-({2-[1-(5-chloro-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 4); plasma desorption LRMS: Calculated for $C_{21}H_{22}ClN_5O_6P$ ($MH^+$): 506.9, Found: 506.2;

2-({2-[1-(1*H*-imidazol[4,5-*c*]pyridin-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 5); plasma desorption LRMS: Calculated for $C_{20}H_{22}N_6O_6P$ ($MH^+$): 473.4, Found: 473.0;

2-({2-[1-(5-carbamoyl-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 6); plasma desorption LRMS: Calculated for $C_{22}H_{24}N_6O_7P$ ($MH^+$): 515.4, Found: 515.2;

2-({2-[1-(5-methylcarbamoyl-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 7); plasma desorption LRMS: Calculated for $C_{23}H_{26}N_6O_7P$ ($MH^+$): 529.5, Found: 529.2;

2-({2-[1-(1*H*-benzoimidazol-2-yl)-ethyl]-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 8); plasma desorption LRMS: Calculated for $C_{20}H_{21}N_5O_6P$ ($MH^+$): 458.4, Found: 458.1;

2-({2-[1-(5-dimethylcarbamoyl-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 9); plasma desorption LRMS: Calculated for $C_{24}H_{28}N_6O_7P$ ($MH^+$): 543.5, Found: 543.1;

3-phosphono-2-({2-[1-(4,6,7-trifluoro-1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-propionic acid (Compound 10); plasma desorption LRMS: Calculated for $C_{21}H_{20}F_3N_5O_6P$ ($MH^+$): 526.4, Found: 526.4;

3-phosphono-2-({2-[1-(5,6-difluoro-1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-propionic acid (Compound 11); plasma desorption

LRMS: Calculated for $C_{21}H_{21}F_2N_5O_6P$ ($MH^+$): 508.4, Found: 508.3;

3-phosphono-2-({2-[1-(5,6,7-trifluoro-1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-propionic acid (Compound 12); plasma desorption LRMS: $C_{21}H_{20}F_3N_5O_6P$ ($MH^+$): 526.4, Found: 526.6;

3-phosphono-2-({2-[1-(5,7-difluoro-1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-propionic acid (Compound 13); plasma desorption LRMS: $C_{21}H_{21}F_2N_5O_6P$ ($MH^+$): 508.4, Found: 508.2;

3-phosphono-2-({2-[1-(4,5,6,7-tetrafluoro-1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-propionic acid (Compound 14); plasma desorption LRMS: $C_{21}H_{19}F_4N_5O_6P$ ($MH^+$): 544.4, Found: 543.4; and

3-phosphono-2-{[2-(4,6,7-trifluoro-1*H*-benzoimidazole-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-propionic acid (Compound 15); plasma desorption LRMS: $C_{20}H_{18}F_3N_5O_6P$ ($MH^+$): 512.4, Found: 512.1.

## EXAMPLE 8

### 2-Benzyloxycarbonylamino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester

A cooled (0° C) mixture of 2-amino-3-phosphonopropionic acid (1.019 g, 6.0 mmol), water (5 mL), and ether (10 mL) was rapidly stirred and treated with benzyl chloroformate (1.3 mL, 9.0 mmol) and 6 N sodium hydroxide (4.5 mL) in four alternating portions. After 16 hours, the organic solvent was removed under reduced pressure, and the residue was added to stirring acetone/methanol (100 mL, 2:1 v/v). The white precipitate that formed was isolated by filtration, rinsed with acetone and dried, to afford the tri-sodium salt of 2-benzyloxycarbonylamino-3-phosphono-propionic acid (2.34 g) This material was dissolved in 0.5 M hydrochloric acid, the solvent was removed under reduced pressure, and the residue so obtained was used directly in the next step.

A suspension of the above material, 2-benzyloxycarbonylamino-3-phosphono-propionic acid, in anhydrous tetrahydrofuran (30 mL) was cooled (0° C) under nitrogen and treated with a diazomethane/ether solution just until a yellow color persisted. The mixture

was allowed to gradually warm to 20° C and stand for 12 hours. The mixture was cooled (0° C), quenched with acetic acid, and diluted with ether. The organic solution was washed with saturated $NaHCO_3$, NaCl, and dried ($Na_2SO_4$). The ether was removed under reduced pressure, to afford 2-benzyloxycarbonylamino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester as a pale yellow oil (1.98 g, 95% yield based on two steps). $C_{14}H_{20}NO_7P$; MW calc. 345.1, found (ES) 346. $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 7.85 (d, 1H), 7.35 (s, 5H), 5.10 (s, 2H), 4.35-4.25 (m, 1H), 3.75-3.50 (m, 9H), 2.30-2.20 (m, 2H).

## EXAMPLE 9

2-Amino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester hydrochloride

A mixture of 2-benzyloxycarbonylamino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester (0.20 g, 0.58 mmol), prepared as in Example 8, and 10% palladium on carbon was suspended in methanol (10 mL) and acidified with 4 M hydrochloric acid in dioxane (0.2 mL). The mixture was hydrogenated at 1 atm for 2 hours. The catalyst was removed by filtration, and the solvent was removed under reduced pressure. The product, 2-amino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester hydrochloride, was obtained as a clear colorless oil (0.13 g, 91% yield). $C_6H_{14}NO_5P\bullet HCl$; $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 6.90 (br s, 3H), 4.00 (m, 1H), 3.80-3.55 (m, 9H), 2.30 (dd, 2H).

## EXAMPLE 10

3,4-Diaminobenzonitrile

A mixture of 4-amino-3-nitrobenzonitrile (2.0 g, 12.3 mmol), anhydrous ethanol (20 mL), and 10% palladium on carbon (approx. 0.5 g), was hydrogenated at 1 atm for 2 hours. The catalyst was removed by filtration, and the solvent was removed under reduced pressure. The product, 3,4-diaminobenzonitrile, was obtained as a tan solid (1.55 g, 95% yield). $C_7H_7N_5$; $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 6.77 (d, 1H), 6.72 (s, 1H), 6.50 (d, 1H), 5.43 (br s, 2H), 4.85 (br s, 2H).

## EXAMPLE 11

5-Cyano-1*H*-benzoimidazol-2-yl-acetic acid ethyl ester

A solution of 3,4-diaminobenzonitrile (1.0 g, 7.5 mmol) and acetic acid (8 mL) was treated under nitrogen with ethoxycarbonimidoyl-acetic acid ethyl ester hydrochloride (1.62 g, 8.3 mmol) , and the mixture was warmed to 85° C. After 3 hours, the mixture was treated with another portion of ethoxy-carbonimidoyl-acetic acid ethyl ester hydrochloride (0.2 g, 1.0 mmol), and heating was continued for 2 hours. The mixture was cooled and poured over cracked ice. The slurry was adjusted to approximately pH 9 with conc. ammonium hydroxide, and a tan solid formed. After allowing the mixture to stir for 1 hours, the product was isolated by filtration, rinsed with water, and dried. 5-Cyano-1*H*-benzoimidazol-2-yl-acetic acid ethyl ester was obtained as a tan powder (1.52 g, 89% yield). $C_{12}H_{11}N_3O_2$; $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 12.90 (br s, 1H), 8.15 (s, 1H), 7.75 (d, 1H), 7.60 (d, 1H), 4.20 (q, 2H), 4.10 (s, 2H), 1.25 (t, 3H).

## EXAMPLE 12

2-(5-Cyano-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carboxylic acid

A solution of 5-cyano-1*H*-benzoimidazol-2-yl-acetic acid ethyl ester (0.60 g, 2.6 mmol), prepared as in Example 11, and 4-amino-3-methylamino-benzoic acid (0.44 g, 2.6 mmol), prepared as in Example 5, in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 2 mL) was degassed briefly under reduced pressure, placed under nitrogen, and heated to 185° C for 3 hours. The resulting brown solution was diluted with an equivalent volume of ethyl acetate and added to stirring anhydrous ether. The tan solid that formed was isolated by filtration, rinsed with ether, and dried.
2-(5-Cyano-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carboxylic acid was obtained as a tan powder (0.95 g crude) and used directly in the next step. $C_{18}H_{13}N_5O_2$; $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 12.90 (br s, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.60 (d, 1H), 7.52 (d, 1H), 4.68 (s, 2H), 3.90 (s, 3H).

EXAMPLE 13

2-{[2-(5-Cyano-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-3-(dimethoxy-phosphoryl)-propionic acid methyl ester

(Compound 16)

A solution of 2-(5-cyano-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carboxylic acid (0.17 g, 0.51 mmol), prepared as in Example 12, 2-amino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester hydrochloride (0.13 g, 0.52 mmol), prepared as in Example 9, and HOBt (0.070 g, 0.52 mmol) in DMF (1.75 mL) was chilled (-40° C) under nitrogen. The mixture was treated with EDC (0.10 g, 0.52 mmol), and *N*,*N*-diisopropylethylamine (0.18 mL, 1.0 mmol), and allowed to gradually warm to 20° C. After 16 hours, the solvent was removed under reduced pressure. The residue was suspended in chloroform, washed with saturated $NaHCO_3$, NaCl, and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the crude material was purified by silica gel chromatography using an isocratic eluant consisting of 90/10/1 chloroform/methanol/acetic acid. The appropriate fractions were pooled, the solvents were removed under reduced pressure and the product, 2-{[2-(5-cyano-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-3-(dimethoxy-phosphoryl)-propionic acid methyl ester was obtained as a white residue (0.10 g, 37%). $C_{24}H_{25}N_6O_6P$: MW calc. 524.2, found (ES) 525.1. $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 13.05 (br s, 1H), 8.88 (d, 1H), 8.15-8.10 (m, 2H), 7.75-6.98 (m, 4H), 4.60 (s, 3H), 3.85 (s, 3H), 3.70-3.55 (m, 9H), 2.60-2.50 (m, 2H).

EXAMPLE 14

2-{[2-(5-Carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-3-phosphonopropionic acid

(Compound 1)

A solution of 2-{[2-(5-cyano-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-3-(dimethoxy-phosphoryl)-propionic acid methyl

ester (0.090 g, 0.17 mmol), prepared as in Example 13, in acetic acid (1 mL) was treated with 40 wt % hydrobromic acid in acetic acid (5 mL). After 6 hours, water (2 mL) was added, and the mixture allowed to stand for 2 days at 20° C. An orange solid was obtained upon dropwise addition of the solution to stirring acetone. The solid was isolated by filtration, rinsed with acetone, and purified by C18 reversed-phase HPLC (2→16% MeCN/$H_2O$ containing 20 mM Hydrochloric acid, over 50 min.). The product, 2-{[2-(5-carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-3-phosphono-propionic acid hydrochloride, was obtained as a pale yellow powder (0.074 g, 83% yield). $C_{21}H_{21}N_6O_7P$: MW calc. 500.1, found (ES) 501.1. $^1$H-NMR (300 MHZ, DMSO-$d_6$) d: 8.85 (d, 1H, J = 8.0 Hz), 8.39 (s, 1H), 8.25 (s, 1H), 7.95 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.4 Hz), 7.85 (d, 2H, J = 207 Hz), 7.78 (m, 2H), 5.19 (s, 2H), 4.25 (m, 1H), 4.03 (s, 3H), 2.35-2.05 (m, 2H).

## EXAMPLE 15

### 2-Ethoxycarbonimidoyl-propionic acid ethyl ester hydrochloride

Ethyl 2-cyanopropionate (100 g 0.29 mol) was dissolved in ethanol (65mL) and the solution cooled to 0° C followed by saturation with dry hydrogen chloride gas. The mixture was allowed to warm to room temperature and stir over 24 hours at which point the reaction was again cooled to 0° C and saturated with hydrogen chloride gas. The mixture was allowed to warm to room temperature and stirred another 24 hours. The imidate salt was precipitated by addition of ethyl ether:hexane (1:1), filtered and dried *in vacuo* to give 2-ethoxycarbonimidoyl-propionic acid ethyl ester hydrochloride (119.6 g 73% yield) as a white solid; $^1$H-NMR (300 MHZ, DMSO-$d_6$): 12.05 (br s, 2H), 4.50 (q, 2H), 4.15 (m, 3H), 1.30 (m, 6H), 1.20 (tr, 3H).

## EXAMPLE 16

2-(3*H*-Imidazo[4,5-*c*]pyridin-2-yl)-propionic acid ethyl ester hydrochloride

3,4-Diaminopyridine (20.0 g 184 mmol) and 2-ethoxycarbonimidoyl-propionic acid ethyl ester hydrochloride (46 g, 220 mmol), prepared as in Example 15, were taken up into glacial acetic acid (100 mL). The mixture was then heated to reflux with stirring for 1.5 hours. The crude material was concentrated *in vacuo* to a thick oil then diluted with ethyl acetate (1L). An insoluble amorphous residue was obtained and the solution was decanted. The ethyl acetate solution was partitioned with saturated aqueous sodium bicarbonate followed by addition of an excess of solid sodium bicarbonate sufficient to neutralize residual acetic acid. Solid sodium chloride was added in sufficient quantity to saturate the aqueous phase which was extracted with ethyl acetate 3x and the organic layers combined. The insoluble residue was then taken into a minimum of water and neutralized by addition of an excess of solid sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate 1x. The organic layer was combined with the previously obtained ethyl acetate solution and the combined ethyl acetate solutions dried over anhydrous magnesium sulfate. Filtration and concentration afforded an orange oil (32g) which slowly crystallized. The hydrochloride salt is obtained by precipitation with ethyl ether and filtration to give 2-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-propionic acid ethyl ester hydrochloride (12.5 g) as a white hygroscopic solid; $^1$H-NMR (300 MHZ, $d_6$-DMSO): 9.40 (s, 1H), 8.59 (d, 1H), 8.15 (d, 1H), 4.40 (q, 1H), 4.05-4.20 (m, 2H), 1.60 (d, 3H), 1.15 (tr, 3H).

## EXAMPLE 17

2-(4,5,6,7-Tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-propionic acid ethyl ester hydrochloride

2-(3*H*-Imidazo[4,5-*c*]pyridin-2-yl)-propionic acid ethyl ester hydrochloride (34.7 g 158 mmol), prepared as in Example 16, was dissolved in trifluoroacetic acid (50 mL) followed by addition of platinum oxide (2.5 g) and the mixture was hydrogenated at 50 psi in

a Parr hydrogenation apparatus for 24 hours. The suspension was filtered and the solution concentrated *in vacuo*. The oily residue was dissolved in a minimum of ethanol followed by addition of dry hydrogen chloride in dioxane solution (4M, 120 mL, 475 mmol). An excess of ethyl ether was added to the acidic solution and the resulting precipitate was collected by filtration and dried *in vacuo* to afford 2-(4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-propionic acid ethyl ester hydrochloride as a hygroscopic white solid (30.7 g 66% yield); $^1$H-NMR (300 MHZ, DMSO-$d_6$): 10.00 (br s, 2H), 4.35 (q, 1H), 4.20 (br s, 2H), 4.10 (m, 2H), 3.35 (m, 2H), 2.90 (br s, 2H), 1.55 (d, 3H), 1.15 (tr, 3H).

## EXAMPLE 18

### 2-(1-Ethoxycarbonyl-ethyl)-1,4,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-5-carboxylic acid benzyl ester

2-(4,5,6,7-Tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-propionic acid ethyl ester hydrochloride (60.2 g, 0.2 mol), prepared as in Example 18, was added to acetonitrile (500 mL) followed by diisopropylethylamine (100 mL, 0.6 mol) and the resulting suspension was cooled to 0° C. Benzyl chloroformate (58 mL, 0.4 mol) was added slowly with stirring and the mixture was slowly warmed to ambient temperature and stirred an additional 16 hours. The mixture was concentrated *in vacuo* followed by addition of ethyl ether (500 mL). The organic solution was washed with 0.1 M aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride then dried over anhydrous sodium sulfate, filtered and the organic solution concentrated to provide a colorless oil. The oil was dissolved in ethanol (320 mL) and the resulting solution cooled to 0° C. Sodium ethoxide in ethanol solution (2.6 M, 85 mL, 0.22 mol) was slowly added to the solution and the mixture was stirred for one hour at 0° C. Hydrogen chloride solution in dioxane (4 M, 50 mL) was added to the solution and the mixture concentrated *in vacuo*. The residue was partitioned with ethyl acetate and saturated aqueous sodium hydrogen carbonate and the organic layer was then washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and filtered. The organic solution was then concentrated in vacuo to provide

2-(1-ethoxycarbonyl-ethyl)-1,4,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-5-carboxylic acid benzyl ester (52 g, 72%) as a yellow amorphous material; $^1$H-NMR (300 MHZ, DMSO-$d_6$): 11.75 (br s, 1H), 7.30 (s, 5H), 5.10 (s, 2H), 4.40 (br s, 2H), 4.05 (m, 2H), 3.75 (q, 1H), 3.65 (br s, 2H), 1.40 (d, 3H), 1.15 (tr, 3H).

## EXAMPLE 19

### 3-Methyl-2-[1-(4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-ethyl]-3*H*-benzoimidazole-5-carboxylic acid hydrochloride

Proceeding as in Example 6 and substituting 2-(1-ethoxycarbonyl-ethyl)-1,4,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-5-carboxylic acid benzyl ester, prepared as in Example 18, for 5-carbamoyl-1*H*-benzimidazol-2-yl-acetic acid ethyl ester affords cyclocondensation product 2-[1-(5-carboxy-1-methyl-1*H*-benzimidazol-2-yl)-ethyl]-1,4,6,7-tetrahydro-3*H*-imidazo[4,5-c]pyridine-5-carboxylic acid benzyl ester as a grey solid. 2-[1-(5-Carboxy-1-methyl-1*H*-benzoimidazol-2-yl)-ethyl]-1,4,6,7-tetrahydro-3*H*-imidazo[4,5-c]pyridine-5-carboxylic acid benzyl ester (911 mg, 2.0 mmol) was dissolved in methanol (25 mL) and the solution added to 10% palladium on carbon under a nitrogen atmosphere. The mixture was hydrogenated at 60 psi using a Parr apparatus for 12 hours. The mixture was then acidified to pH 2 by dropwise addition of 4 M hydrogen chloride in dioxane solution and filtered. The organic solution was concentrated *in vacuo* to afford 3-methyl-2-[1-(4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-ethyl]-3*H*-benzoimidazole-5-carboxylic acid hydrochloride (725 mg, 100%) as an orange solid; plasma desorption LRMS: Calculated for $C_{17}H_{20}N_5O_2$ ($MH^+$): 326.4, Found: 326.2.

EXAMPLE 20

2-({2-[1-(5-Acetyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid

(Compound 18)

3-Methyl-2-[1-(4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-ethyl]-3*H*-benzoimidazole-5-carboxylic acid hydrochloride (61 mg, 0.17 mmol), prepared as in Example 19, was taken up into DMF (1.0 mL) followed by addition of diisopropylethylamine (0.5 mmol, 0.09 mL) and the solution was cooled to 0° C. Acetic anhydride (0.17 mmol, 0.016 mL) was added and the mixture was stirred an additional 5 minutes at 0° C then warmed to ambient temperature and concentrated *in vacuo*. The residue was taken into methanol (0.5 mL) followed by addition of an excess of ethyl ether. The organic solution was decanted from the insoluble residue and the precipitation process was repeated once. The residue was then dried *in vacuo*, taken into DMF (1.0 mL) and the solution cooled to 0° C. Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP, 79 mg, 0.17 mmol) was added to the solution and stirred an addition 15 minutes at 0° C. Diisopropylethylamine (0.18 mL, 1.0 mmol) was added followed by 2-amino-3-phosphonopropionic acid (29 mg, 0.17 mmol) and the suspension was warmed to 55° C for 12 hours. The mixture was concentrated *in vacuo* then taken into 5% aqueous acetonitrile and the solution was filtered. The coupled product was purified by preparative reverse phase HPLC. Lyophillization of the pure fractions afforded 2-({2-[1-(5-acetyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid as a white amorphous solid; plasma desorption LRMS: Calculated for $C_{22}H_{28}N_6O_7P$ ($MH^+$): 519.5, Found: 519.3.

Proceeding as in Example 20 and substituting different reagents the following compounds of the invention were prepared:

2-({2-[1-(5-benzyloxycarbonyl-4,5,6,7-tetrahydro-

1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 19); plasma desorption LRMS: $C_{28}H_{32}N_6O_8P$ ($MH^+$): 611.6, Found: 610.8;

2-({2-[1-(5-methylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 20); plasma desorption LRMS: $C_{22}H_{28}N_7O_7P$ ($MH^+$): 534.5, Found: 534.2;

2-({2-[1-(5-dimethylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 21); plasma desorption LRMS: $C_{23}H_{30}N_7O_7P$ ($MH^+$): 548.5, Found: 548.2;

2-({2-[1-(5-benzylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 22); plasma desorption LRMS: $C_{28}H_{32}N_7O_7P$ ($MH^+$): 609.6, Found: 610.3;

2-({2-[1-(5-*tert*-butylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 23); plasma desorption LRMS: $C_{25}H_{34}N_7O_7P$ ($MH^+$): 575.6, Found: 576.4; and

2-({2-[1-(5-hexylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 24); plasma desorption LRMS: $C_{27}H_{38}N_7O_7P$ ($MH^+$): 603.6, Found: 604.6.

## EXAMPLE 21

### 2-(1*H*-Benzoimidazol-2-yl)-propionic acid ethyl ester

*o*-Phenylenediamine (11.0 g, 0.10 mol) and 2-ethoxycarbonimidoyl-propionic acid ethyl ester (25.5 g, 0.12 mol), prepared as in Example 14, were combined in acetic acid (30 mL) with cooling sufficient to maintain a temperature of 20° C. The mixture was

allowed to stir for 3 hours, then poured over cracked ice. The slurry was brought to pH 10-11 with $K_2CO_3$, and stirred for 3 hours to allow for crystallization. The solid material was isolated by filtration, rinsed with water and dried. 2-(1*H*-benzoimidazol-2-yl)-propionic acid ethyl ester was obtained as a tan solid (20.55 g, 93%): $^1$H-NMR (300 MHz, DMSO-$d_6$) d: 12.45 (br s, 1H), 7.50 (m, 2H), 7.15 (m, 2H), 4.10 (m, 3H), 1.52 (d, 3H), 1.12 (t, 3H).

EXAMPLE 22

2-[1-(1*H*-Benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carboxylic acid

A solution of 2-(1*H*-benzoimidazol-2-yl)-propionic acid ethyl ester (4.00 g, 18 mmol), prepared as in Example 21, and 4-amino-3-methylaminobenzoic acid (3.05 g, 18 mmol), prepared as in Example 5, in DMPU (9 mL) was heated at 185° C for 2h. The mixture was cooled and diluted with an equivalent volume of ethyl acetate, and then added gradually to stirring ether. The green precipitate which formed was isolated by filtration, rinsed with ether, and subsequently reprecipitated from warm methanol/ether. The new precipitate was isolated and dried. 2-[1-(1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carboxylic acid was obtained as a pale green powder (3.33 g, 57%): $^1$H-NMR (300 MHz, DMSO-$d_6$) d: 12.8 (br s, 1H), 12.4 (br s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.5 (m, 2H), 7.1 (m, 2H), 4.9 (q, 1H), 3.8 (s, 3H), 1.8 (d, 3H).

EXAMPLE 23

2-({2-[1-(1*H*-Benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-(dimethoxy-phosphoryl)-propionic acid methyl ester

(Compound 17)

A solution of 2-[1-(1*H*-Benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carboxylic acid (0.19 g, 0.59 mmol), prepared as in Example 22, 2-amino-3-(dimethoxy-phosphoryl)-propionic acid methyl ester hydrochloride (0.17 g, 0.69 mmol), prepared as in Example 9, and HOBt (0.088 g, 0.65 mmol) in DMF (2.4 mL) was chilled (-50° C) under

nitrogen. The mixture was treated with EDC (0.13 g, 0.68 mmol), and *N,N*-diisopropylethylamine (0.40 mL, 2.3 mmol), and allowed to gradually warm to 20° C. After 16 hours, the solvent was removed under reduced pressure. The residue was suspended in ethyl acetate, washed with saturated $NaHCO_3$, NaCl, and dried ($Na_2SO_4$). The solvent was removed under reduced pressure. 2-({2-[1-(1*H*-Benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-(dimethoxy-phosphoryl)-propionic acid methyl ester was obtained as a golden amorphous residue and used directly in the next step without further purification: $C_{24}H_{28}N_5O_6P$: MW calc. 513.2, found (ES) 514.2. $^1$H-NMR (300 MHz, DMSO-$d_6$) d: 8.9 (d, 1H), 7.9 (s, 1H), 7.7 (d, 1H), 7.6 (d, 1H), 7.4 (m, 2H), 7.2 (m, 2H), 4.9 (q, 1H), 4.7 (m, 1H), 3.8 (s, 3H), 3.7-3.5 (m, 9H), 2.5-2.3 (m, 2H), 1.8 (d, 3H).

## EXAMPLE 24

## 2-({2-[1-(1*H*-Benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid

## (Compound 25)

The entire quantity of 2-({2-[1-(1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-(dimethoxy-phosphoryl)-propionic acid methyl ester prepared in Example 23 was dissolved in acetic acid (2 mL) and treated with 40 wt% of hydrobromic acid in acetic acid (2 mL). After 5 hours, water (1 mL) was added and the mixture was allowed to stand for 12 hours. Another 40 wt % hydrobromic acid of 40 wt % in acetic acid (2 mL) was added, and the mixture allowed to stand 24 hours. The solution was added to stirring ethyl acetate, and a brown solid was isolated by filtration and rinsed with ethyl acetate. The material was purified by C18 reversed-phase HPLC (2→27% MeCN/$H_2O$ containing 0.1% TFA, over 50 min.). Appropriate fractions were pooled, and the solvent was removed under reduced pressure. The product was re-lyophilized from 0.1 M Hydrochloric acid. 2-({2-[1-(1*H*-Benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid hydrochloride was obtained as a pale yellow powder (0.14 g, 45%): $C_{21}H_{22}N_5O_6P$: MW calc. 471.1, found (ES) 472.1. $^1$H-NMR (300

MHz, DMSO-$d_6$) d: 8.74 (d, 1H, J = 9 Hz), 8.23 (s, 1 H), 7.80-7.60 (m, 4 H), 7.55-7.50 (m, 2H), 5.42 (q, 1H, J = 9 Hz), 4.60 (m, 1H), 4.00 (s, 3H), 2.30-2.10 (m, 2H), 1.96 (d, 3H, J = 9 Hz).

Proceeding as in Example 24 and sustituting different starting materials the following compounds of the invention were prepared:

2-({2-[1-(1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid methyl ester (Compound 26); ES LRMS: $C_{22}H_{25}N_5O_6P$ ($MH^+$): 486.2, Found: 486.1;

3-({2-[1-(1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid (Compound 27); ES LRMS: $C_{21}H_{23}N_5O_6P$ ($MH^+$): 472.1, Found: 472.1;

[2-({2-[1-(1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-ethyl]-phosphonic acid (Compound 28); ES LRMS: $C_{20}H_{23}N_5O_4P$ ($MH^+$): 428.1, Found: 428.1; and

(*R*)-2-({2-[1-(1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-sulfo-propionic acid (Compound 29); ES LRMS: $C_{21}H_{22}N_5O_6S$ ($MH^+$): 472.1, Found: 472.2.

## EXAMPLE 25

### *In vitro* HCV-NS3 Protease Inhibition Assay

A mixture of HCV NS3 protease (1 to 3 nM), NS3 cofactor NS4a (10 μM), $ZnCl_2$ (5 μM), Tris (50 mM; pH 7.5), glycerol (50%), TWEEN-20® (polyoxyethylenesorbitan monolaurate; 0.05%) and test compound (varying concentrations) was incubated for 15 minutes at room temperature (21 to 24 °C) in 96-well microtiter plates. The quenced fluorescence substrate acetyl-Asp-Glu-Asp(Edans)-Glu-Glu-Abu-Ψ[COO]-Ala-Ser-Lys(Dabcyl)-$NH_2$ (AnaSpec, Inc., San Jose, CA, U.S.A.) was added to a final concentration

of 1.5 μM. The hydrolysis of the fluorescent substrate was followed spectrophotometrically at 485 nanometers after excitation at 355 nanometers (Taliani, M., Bianchi, E., Narjes, F., Fossatelli, M., Urbani, C.S., De Francesco, R., and Pessi, A., (1996) *Anal. Biochem.* 240, 60-67).

The velocity of the NS3 catalyzed hydrolysis was determined from the linear portion of the progress curves using a fMax Microplate Reader (Molecular Devices, Sunnyvale, CA, U.S.A.) interfaced with a Macintosh PowerPC computer. Apparent inhibition constants ($K_i$) were calculated from the progress curves using the software package Batch $K_i$ (Biokin Ltd., Madison, WI, (Kuzmic, P. (1996) *Anal. Biochem.* 237, 260273) which provides a parametric method for determining inhibitor potency using a transformation of a tight binding inhibition model (Morrison, J.F. (1969) *Biochem. Biophys. Acta* 185, 269-286).

Proceeding as described in Example 25 or by methods known to those of ordinary skill, the following compounds of the invention were tested for HCV-NS3 protease inhibitory activity:

(Compound 1, $K_i$ = 0.062 μM), (Compound 2, $K_i$ = 0.582 μM), (Compound 3, $K_i$ = 0.745 μM), (Compound 6, $K_i$ = 0.621 μM), (Compound 14, $K_i$ = 0.822 μM) and (Compound 25, $K_i$ = 0.233 μM).

EXAMPLE 26

The following are representative pharmaceutical formulations containing a compound of the invention.

ORAL FORMULATION

| | |
|---|---|
| Compound of the Invention | 10-100 mg |
| Citric Acid Monohydrate | 105 mg |
| Sodium Hydroxide | 18 mg |
| Flavoring | |
| Water | q.s. to 100 mL |

INTRAVENOUS FORMULATION

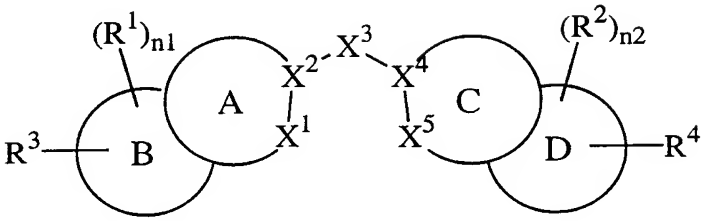
| | |
|---|---|
| Compound of the Invention | 0.1-10 mg |
| Dextrose Monohydrate | q.s. to make isotonic |
| Citric Acid Monohydrate | 1.05 mg |
| Sodium Hydroxide | 0.18 mg |
| Water for Injection | q.s. to 1.0 mL |

TABLET FORMULATION

| | |
|---|---|
| Compound of the Invention | 1% |
| Microcrystalline Cellulose | 73% |
| Stearic Acid | 25% |
| Colloidal Silica | 1%. |

WE CLAIM:

1. A compound of Formula I:




I

in which:

n1 is 0, 1, 2, 3 or 4;

n2 is 0, 1, 2 or 3;

A together with B comprise a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom moiety, $X^1$ and $X^2$ are adjacent annular members of an aromatic ring and $X^1$ is a heteroatom moiety selected from –N=, –$NR^5$–, –O– and –S–, wherein $R^5$ is hydrogen or ($C_{1-6}$)alkyl;

C together with D comprise a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, $X^4$ and $X^5$ are adjacent annular members of an aromatic ring and $X^5$ is a heteroatom moiety selected from –N=, –$NR^6$–, –O– and –S–, wherein $R^6$ is hydrogen or ($C_{1-8}$)alkyl optionally substituted with one to two substituents independently selected from halo, tri($C_{1-6}$)alkylammonio, –$NR^7R^7$, –C(O)$NR^7R^7$, –$OR^7$, –C(O)$OR^7$, –OC(O)$R^7$ or –$S(O)_2OR^7$, wherein $R^7$ at each occurrence independently is hydrogen or ($C_{1-6}$)alkyl;

$X^3$ is –O–, –S–, –S(O)–, –$S(O)_2$–, –C(O)–, –$NR^8$– or –$CR^8R^9$–, wherein $R^8$ is hydrogen, halo, ($C_{1-6}$)alkyl or together with $R^9$ forms ($C_{2-6}$)alkylene or ($C_{1-6}$)alkylidene and $R^9$ is hydrogen, halo, ($C_{1-6}$)alkyl or as defined above, wherein any 1 to 3 carbon atoms with a free valence comprising $R^8$ and/or $R^9$ optionally independently are substituted with halo,

tri($C_{1-6}$)alkylammonio, $-NR^{10}R^{10}$, $-C(O)NR^{10}R^{10}$, $-OR^{10}$, $-C(O)OR^{10}$ or $-OC(O)R^{10}$, wherein $R^{10}$ at each occurrence independently is hydrogen or ($C_{1-6}$)alkyl;

$R^1$ at each occurrence independently is ($C_{1-6}$)alkyl, ($C_{1-6}$)alkyloxy, ($C_{1-6}$)alkanoyloxy, ($C_{1-6}$)alkylthio, halo, hydroxy or mercapto and bonded to any annular carbon atom with a free valence comprising B;

$R^2$ at each occurrence independently is ($C_{1-6}$)alkyl, ($C_{1-6}$)alkyloxy, ($C_{1-6}$)alkanoyloxy, ($C_{1-6}$)alkylthio, halo, hydroxy or mercapto and bonded to any annular carbon atom with a free valence comprising C;

$R^3$ is cyano, $-R^{11}$, $-CR^{12}R^{12}NR^{11}R^{13}$, $-C(NR^{13})R^{11}$, $-C(O)R^{11}$, $-C(NR^{13})NR^{11}R^{13}$, $-C(O)NR^{11}R^{13}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^{11}R^{13}$ or $-S(O)_2OR^{11}$ and bonded to any annular atom with a free valence comprising B, wherein:

$R^{11}$ is hydrogen, ($C_{1-6}$)alkyl, cyclo($C_{3-6}$)alkyl($C_{0-3}$)alkyl, heterocyclo($C_{3-6}$)alkyl($C_{0-3}$)alkyl, ($C_{6-10}$)aryl($C_{0-3}$)alkyl, hetero($C_{5-14}$)aryl($C_{0-3}$)alkyl, polycyclo($C_{9-10}$)aryl($C_{0-3}$)alkyl or heteropolycyclo($C_{8-10}$)aryl($C_{0-3}$)alkyl; wherein any alkyl moiety comprising $R^{11}$ optionally independently is substituted with 1 to 3 substitutents selected from $-P(O)(OR^{14})OR^{14}$, $-S(O)_2OR^{14}$ and $-C(O)OR^{14}$ and any 1 to 3 annular carbon atoms with free valences of any aromatic ring comprising $R^{11}$ optionally independently are substituted with halo, nitro, cyano, optionally halo-substituted ($C_{1-6}$)alkyl, $-OR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-X^6NR^{14}R^{14}$, $-X^6NR^{14}C(O)NR^{14}R^{14}$ or $-X^6NR^{14}C(NR^{14})NR^{14}R^{14}$, wherein $X^6$ is a bond or methylene and $R^{14}$ at each occurrence independently is hydrogen or ($C_{1-6}$)alkyl,

$R^{12}$ at each occurrence independently is hydrogen, ($C_{1-3}$)alkyl or together with another $R^{12}$ and the carbon atom to which both are attached forms cyclopropyl and

$R^{13}$ at each occurrence independently is hydrogen or ($C_{1-6}$)alkyl; and

$R^4$ is $-R^{15}$, $-OR^{15}$, $-NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2OR^{15}$, $-S(O)_2NR^{15}R^{16}$, $-N(R^{16})S(O)_2R^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-N(R^{16})C(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-N(R^{16})C(O)OR^{15}$ or $-N(R^{16})C(O)NR^{15}R^{16}$, and bonded to any annular carbon atom with a free valence comprising C, wherein:

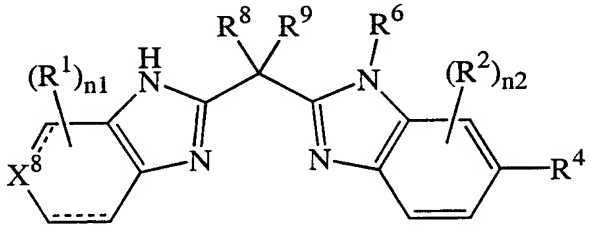
$R^{15}$ is ($C_{1-6}$)alkyl substituted with 1 to 2 radicals selected from

$-P(O)(OR^{17})OR^{17}$ and $-S(O)_2OR^{17}$ and optionally substituted with 1 to 2 $-C(O)OR^{17}$ groups, wherein $R^{17}$ is hydrogen or $(C_{1-6})$alkyl, and

$R^{16}$ is hydrogen or $(C_{1-6})$alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

2. The compound of Claim 2 in which A together with B and C together with D comprise fused heterobicyclic radicals wherein A and C each contain 5 annular members and B and D each contain 6 annular members and $X^1$ and $X^2$ and $X^4$ and $X^5$ are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

3. A compound of Formula II:



II

in which:

the dashed lines independently represent optional bonds;

n1 is 0, 1, 2, 3 or 4;

n2 is 0, 1, 2 or 3;

$X^8$ is C, N, $CR^3$ or $NR^3$, wherein $R^3$ is cyano, $(C_{1-6})$alkyl, $-C(O)R^{11}$, $-C(O)NR^{11}R^{13}$ or $-C(O)OR^{11}$, wherein $R^{11}$ independently is hydrogen, $(C_{1-6})$alkyl or $(C_{1-4})$aryl$(C_{0-4})$alkyl, $R^{13}$ is hydrogen or $(C_{1-6})$alkyl and any alkyl moiety comprising $R^{11}$ optionally independently is substituted with 1 to 3 substitutents selected from $-P(O)(OR^{14})OR^{14}$, $-S(O)_2OR^{14}$ and $-C(O)OR^{14}$, wherein $R^{14}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl;

provided that when $X^8$ is $NR^3$ the adjacent optional bond is not present and, unless indicated otherwise, any free valence of an annular atom is attached to a hydrogen atom;

$R^1$ and $R^2$ at each occurrence independently are $(C_{1-6})$alkyl, $(C_{1-6})$alkyloxy, halo or hydroxy and bonded to any annular carbon atom with a free valence;

$R^4$ is $-C(O)NR^{15}R^{16}$, wherein:

$R^{15}$ is $(C_{1-6})$alkyl substituted with 1 to 2 radicals selected from $-P(O)(OR^{17})OR^{17}$ and $-S(O)_2OR^{17}$ and optionally substituted with 1 to 2 $-C(O)OR^{17}$ groups, wherein $R^{17}$ is hydrogen or $(C_{1-6})$alkyl, and

$R^{16}$ is hydrogen or $(C_{1-6})$alkyl;

$R^6$ is $(C_{1-6})$alkyl optionally substituted with one to two substituents independently selected from halo, tri$(C_{1-6})$alkylammonio, $-NR^7R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-C(O)OR^7$, $-OC(O)R^7$ or $-S(O)_2OR^7$, wherein $R^7$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl; and

$R^8$ and $R^9$ independently are hydrogen, halo or $(C_{1-6})$alkyl, wherein any 1 to 3 carbon atoms with a free valence comprising $R^8$ and/or $R^9$ optionally independently are substituted with halo, tri$(C_{1-6})$alkylammonio, $-NR^{10}R^{10}$, $-C(O)NR^{10}R^{10}$, $-OR^{10}$, $-C(O)OR^{10}$ or $-OC(O)R^{10}$, wherein $R^{10}$ at each occurrence independently is hydrogen or $(C_{1-6})$alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 in which both of the optional bonds are present, n1and n2 each are 0, $X^8$ is N or $CR^3$, $R^6$ is $(C_{1-4})$alkyl, $R^8$ is hydrogen or methyl and $R^9$ is hydrogen; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

5. The compound of Claim 4 in which $R^3$ is acetyl, benzyloxycarbonyl, cyano or $-C(O)NR^{11}R^{13}$, wherein $R^{11}$ and $R^{13}$ independently are hydrogen or methyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

6. The compound of Claim 3 in which neither of the optional bonds are present, n1and n2 are 0, $X^8$ is $NR^3$, $R^6$ is $(C_{1-4})$alkyl, $R^8$ is hydrogen or methyl and $R^9$ is hydrogen; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

7. The compound of Claim 6 in which $R^3$ is acetyl, benzyloxycarbonyl or $-C(O)NR^{11}R^{13}$, wherein $R^{11}$ and $R^{13}$ independently are hydrogen or methyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

8. The compound of Claim 3 in which both of the optional bonds are present, n1 is 0, 1, 2, 3 or 4; n2 is 0; $X^8$ is C; $R^1$ at each occurrence is chloro, fluoro or hydroxy; $R^6$ is $(C_{1-4})$alkyl; $R^8$ is hydrogen or methyl; and $R^9$ is hydrogen; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

9. The compound of Claim 5 in which $X^8$ is $CR^3$, wherein $R^3$ is carbamoyl, $R^4$ is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ is methyl and $R^8$ and $R^9$ are hydrogen, namely 2-{[2-(5-carbamoyl-1*H*-benzoimidazol-2-ylmethyl)-3-methyl-3*H*-benzoimidazole-5-carbonyl]-amino}-phosphono-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

10. The compound of Claim 5 in which $X^8$ is $CR^3$, wherein $R^3$ is carbamoyl, $R^4$ is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ and $R^8$ are methyl and $R^9$ is hydrogen, namely 2-({2-[1-(5-carbamoyl-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

11. The compound of Claim 7 in which $R^3$ is methylcarbamoyl, $R^4$ is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ and $R^8$ are methyl and $R^9$ is hydrogen, namely 2-({2-[1-(5-methylcarbamoyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

12. The compound of Claim 8 in which n1 is 0, $R^4$ is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ and $R^8$ are methyl and $R^9$ is hydrogen, namely 2-({2-[1-(1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

13. The compound of Claim 8 in which n1 is 1, $R^1$ is fluoro, $R^4$ is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ and $R^8$ are hydrogen and $R^9$ is hydrogen, namely 2-({2-[1-(5-fluoro-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

14. The compound of Claim 8 in which n1 is 1, $R^1$ is hydroxy, $R^4$ is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ and $R^8$ are methyl and $R^9$ is hydrogen, namely 2-({2-[1-(5-hydroxy-1*H*-benzoimidazol-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-3-phosphono-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

15. The compound of Claim 8 in which n1 is 4, $R^1$ at each occurrence is fluoro, $R^4$

is 2-phosphono-1-carboxyethylcarbamoyl, $R^6$ and $R^8$ are methyl and $R^9$ is hydrogen, namely 3-phosphono-2-({2-[1-(4,5,6,7-tetrafluoro-1*H*-benzoimidazole-2-yl)-ethyl]-3-methyl-3*H*-benzoimidazole-5-carbonyl}-amino)-propionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition which contains a compound of Claim 1 or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

17. A pharmaceutical composition which contains a compound of Claim 3 or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

18. A method of treating a patient infected with hepatitis C virus, which method comprises administering to the patient a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

19. A method of treating a patient infected with hepatitis C virus, which method comprises administering to the a patient therapeutically effective amount of compound of Claim 3 or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22850

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : C07D 235/04, 235/06, 235/20
US CL :514/394; 548/305.7, 335.1
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/394; 548/305.7, 335.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5,693,515 A (CLARK et al) 02 December 1997, col. 5, lines 50-60 and col. 10, table 1. | 1, 2 and 16 |
| X | US 3,210,370 A (URSPRUNG, J.J.) 05 October 1965, col. 6, lines 5-14 and example 20. | 1, 2 and 16 |
| X,P | WO 98/452275 A1 (AXYS PHARMACEUTICALS CORPORATION.) 15 October 1998, see whole document. | 1-5, 8-10, and 12-19 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>21 DECEMBER 1999 | Date of mailing of the international search report<br>02 FEB 2000 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>CHANA AULAKH<br>Telephone No. (703) 308-1235 |

Form PCT/ISA/210 (second sheet)(July 1992)★

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22850

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
8, 12-15 and in part for 1-5, 9, 10 and 16-19

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22850

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

I. Compounds of formula I where either ring A, B, C or D is a seven-membered ring containing atleast one N atom as the heteroatom, clasiified in class 540.

II. Compounds of formula I where either ring A, B, C or D is a 6-membered ring containing atleast one N atom as the heteroatom, classified in class 546.

III. Compounds of formula I where either ring A, B, C or D is a 5-7-membered ring containing only O or S as the heteroatoms, classified in class 549.

IV. Compounds of formula I where either ring A, B, C or D is a 5-membered ring containing only 3-4 nitrogens as heteroatoms, classified in class 548, subclass 250+.

V. Compounds of formula I where either ring A, B, C or D is a 5-membered ring containing atleast one N and one S or O as the heteroatoms, classified in class 548, subclass 100+.

VI. Compounds of formula I where either ring A, B, C or D is a 5-membered ring containing only 2 nitrogens as heteroatoms, classified in class 548, subclass 300.1+.

VII. Compounds of formula I where either ring A, B, C or D is a 5-membered ring containing only one N as the heteroatom, classified in class 548, subclass 400+.

The claims are deemed to correspond to the species listed above in the following manner:

Species VI : Claims 8 and 12-15.

Species II : Claims 6, 7 and 11.

The following claims are generic: 1-5, 9, 10 and 16-19.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:
There is no common core which in the Markush Practice, is a significant structural element shared by all the alternatives; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1).